CLINICOPATHOLOGICAL CHARACTERISTIC OF LUPUS NEPHRITIS : A CASE SERIES AND LITERATURE REVIEW

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ABSTRAK

Lupus nefritis (LN) merupakan salah satu manifestasi klinis dari penyakit Lupus Sistemik Eritematosus (LES) yang disebabkan oleh proses peradangan yang timbul akibat terganggunya mekanisme imunologis penderitanya. Penelitian ini memuat 5 kasus LN dimana setiap pasien menunjukkan karakteristik klinikopatologi yang bervariasi setelah dilakukan analisa terstruktur terhadap data rekam medis pasien. Hasil penelitian ini menunjukkan bahwa sebagian besar pasien LN adalah perempuan. Melalui temuan ini didapatkan adanya kemungkinan hubungan antara respon imun yang meningkat dengan hormon estrogen pada perempuan. Penderita LN dapat tampil dengan keluhan terkait abnormalitas urin seperti urin yang berbusa, namun pasien LN juga dapat tampil dengan gejala klasik LN seperti edema periorbital maupun perifer. Gejala klinis lainnya yang dapat timbul pada pasien LN antara lain mual, muntah, sesak nafas, dan adanya tanda-tanda anemia. Pengukuran kreatinin, ureum, dan laju filtrasi glomerulus (LFG) penting dilakukan untuk mengevaluasi fungsi ginjal pasien LN. Terdapat hubungan antara temuan laboratorium dan gejala klinis yang tampil pada pasien. Hasil pemeriksaan histopatologi menunjukkan sebagian besar pasien terklasifikasi dalam LN Kelas II. Pemeriksaan histopatologi adalah pemeriksaan penunjang yang paling tepat untuk menentukan tipe lesi ginjal pada pasien LN. Sulitnya menegakkan diagnosis LN pada tahap awal perjalanan penyakit membutuhkan perhatian lebih. Untuk itu, perlu dilakukan pemeriksaan dan analisa karakteristik klinikopatologi yang terstruktur sejak tahap awal perjalanan penyakit agar tercapainya prognosis yang lebih baik bagi pasien.

Kata kunci : glomerulonefritis, lupus nefritis, lupus sistemik eritematosus

ABSTRACT

Lupus nephritis (LN) is one of the clinical manifestations of systemic lupus erythematosus (SLE) disease. LN is caused by an inflammation process, because there is a presence of an immunological impairment. We studied 5 cases of LN. Each patient shows different clinical features in each case. Laboratory examination in each patient also shows quite varied results. In this case series, the sex data of the patients shows that there might be a relation between escalated immune response and estrogens hormone in females Other clinical features that might be present in LN patients are nausea, vomiting, dyspnea, and anemia. Creatinine, blood urea, and glomerular filtration rate (GFR) measurement is important to evaluate kidney function. The pathological examination also shows that the majority type of LN in this case is LN Class II. Pathological examination is the most correct way to determine the type of kidney lesion. Clinical features, laboratory, and histopathological profile in LN patients may vary depending on the onset of the disease. Laboratory findings can be associated with the clinical features that are present in LN patients. The difficulty of making the diagnosis of LN in the early process requires more attention because it is important in order to improve the prognosis of LN.

***Keywords** : glomerulonephritis, lupus nephritis, systemic lupus erythematosus*

INTRODUCTION

Lupus nephritis (LN) is one of the clinical manifestations of systemic lupus erythematosus (SLE) disease. SLE is a chronic autoimmune disease characterized by an inflammation process

that cause damage to multiple organ because the presence of autoantibodies, dysregulation of cytokines and autoreactive B and T cells.(Alduraibi & Tsokos, 2024) In the most of the SLE cases, patient will develop LN in 5 years after the first onset of SLE.(Musa et al., 2024) Epidemiological data shows that 50-60% SLE patients in Asia have kidney involvement in the course of the disease. This percentage is higher than the percentage in Caucasian SLE patient.(Yap & Chan, 2015) Genetic predisposing factors play a significant role in the pathogenesis of SLE and LN.(Obrișcă et al., 2021) Interaction between autoreactive B and T cells also plays an important role. B cells involved in the presentation of antigen associated with dendritic cells and the production of antibodies. In addition, T cells will stimulate B cells autoreactivity and autoantibodies production. T cells also produce the cytokines such as interleukin-17 (IL-17) that are important in the process of developing LN.(Anders et al., 2020)

In addition to B cells and T cells, the type I interferon (IFN) system has an additional important role in the pathogenesis of SLE and LN.(Obrișcă et al., 2021) A signalling system through type I IFN receptor is a molecular characteristic of SLE and LN that will dysregulates the immune system and also cause damage to the kidney cells.(Mohan & Putterman, 2015) In the early phase of the disease, patients with LN are often not present with atypical clinical features. LN is more often found in urine and laboratory examination.(Parikh et al., 2020) This study will present a case series of 5 patients with LN and illustrate the clinical features and laboratory finding as well as the histopathological profile in LN patients.

CASE PRESENTATION

In this study, we reported 5 cases of LN obtained from patients who came to the Kidney and Hypertension Clinic at K.R.M.T Wongsonegoro Regional Public Hospital Semarang. Patients show different clinical features in each case. Some laboratory examinations consisting of the measurements of urea level, serum creatinine, albumin, estimated glomerular filtration rate (eGFR) and proteinuria in each patient also show quite varied results. Case 1: A 18-year-old male, presented to the clinic with a complaint of right flank pain. His urea level was 81.4 mg/dL and serum creatinine was 0.8 mg/dL. The assessment of his albumin level showed a value of 3.1 g/dL and his eGFR was 132 mL/min/1.73 m^2. Urinalysis result showed positive (2+) protein in the urine. From his renal biopsy results, he was diagnosed with unclassified LN.

Case 2: A 19-year-old female, presented with peripheral edema, anemic conjunctiva, nausea, and vomiting. Patient's blood urea level was 298.5 mg/dL, serum creatinine 3.8 mg/dL, albumin 1.39 g/dL, eGFR 17 mL/min/1.73 m^2 with positive (1+) protein in the urine. Her renal biopsy revealed focal segmental mesangial proliferation in some glomeruli. She was diagnosed with class II LN. Case 3: A 33-year-old female, who presented with clinical features of periorbital edema and peripheral edema. Based on the laboratory findings, her urea level was 22.5 mg/dL, serum creatinine 0.9 mg/dL, albumin level 3.7 g/dL, eGFR 87 mL/min/1.73 m^2 and urinalysis showed positive (2+) protein in the urine. The renal biopsy revealed hypercellular mesangial with focal segmental proliferation in some glomeruli. She was diagnosed with class II LN.

Case 4: A 64-year-old male, presented with a history of peripheral edema, nausea, and dyspnea. His urea level was 118.9 mg/dL and his serum creatinine was 3.5 mg/dL. Patient's albumin was 3.1 g/dL and eGFR 19 mL/min/1.73 m^2. Urinalysis showed positive (3+) protein in the urine. His histopathological result from the renal biopsy showed a focal segmental mesangial lesion in some glomeruli. He was diagnosed with class II LN. Case 5: A 31-year-old female, presented with foamy urine, peripheral edema, fatigue and weakness, loss of appetite, nausea, and vomiting. From the laboratory examinations her urea level was 132.2 mg/dL, serum creatinine 2.8 mg/dL, albumin27 g/dL and eGFR 22 mL/min/1.73 m^2. Urinalysis showed a positive (3+) protein in the urine. Her renal biopsy result showed glomerulus

adhesions with hypercellular appearance, focal sclerosis and crescent appearance, and a visible closure of capillary lumen. She was diagnosed with class IV-S(A) LN (table 1).

Table 1. Clinical Features, Laboratory and Histopathology Findings of Five LN Patients

No.	Sex	Age	Clinical Features	Laboratory Findings					Histopathology Findings	Types of Nephrotic Syndrome
				Ureum (mg/dL)	Creatinine (mg/dL)	Albumin (g/dL)	Proteinuria	eGFR (mL/min/1.73 m2)		
Single Nephrotic Syndrome										
1	M	18	Right Flank Pain	81.4	0.8	3.1	POS (2+)	132	N/A	Lupus Nephritis Unclassified
2	F	19	- Peripheral Edema - Anemic Conjunctiva - Nausea - Vomiting	298.5	3.8	1.3	POS (1+)	17	Focal segmental mesangial proliferation in some glomeruli.	Lupus Nephritis Class II
3	F	33	- Peripheral Edema - Periorbital Edema	22.5	0.9	3.7	POS (2+)	87	Hypercellular mesangial with focal segmental mesangial proliferation in some glomeruli.	Lupus Nephritis Class II
4	M	64	- Peripheral Edema - Dyspnea - Nausea	118.9	3.5	3.1	POS (3+)	19	Focal segmental mesangial lesion in some glomeruli.	Lupus Nephritis Class II
5	F	31	- Foamy Urine - Peripheral Edema - Fatigue & Weakness - Nausea - Vomiting	132.2	2.8	2.7	POS (3+)	22	- Glomerulus adhesions with hypercellular appearance. - Focal sclerosis and crescent appearance. - Visible closure of capillary lumen.	Lupus Nephritis Class IV-S(A)

DISCUSSION

Plenteous studies bring up the relation between estrogens and autoimmune in females. There's a significant difference between male and female prevalence in patients with SLE because from the reported studies, approximately 4-20% of SLE patients are male.(Schwartzman-Morris & Putterman, 2012) In this case series, 60% of the patients are female and the other 40% are male. This number of prevalence might be related to the other studies that noted the effect of estrogens can also escalate autoimmune response in females. In the population of patients with SLE, renal disease develops in 60% of the patients globally and it is a source of major morbidity and mortality because the disease can rapidly progressing into an end-stage renal disease.(Schwartzman-Morris & Putterman, 2012) LN can be characterized by mild proteinuria and other urinary abnormalities. But clinical presentation may be silent with urinalysis, renal function, and 24-h proteinuria remains within the normal range.(Gasparotto et al., 2020) Typically, some patients with LN may present with foamy urine. Foamy urine is the early signs of proteinuria that indicate tubular and glomerular dysfunction in SLE patient.(Musa et al., 2024) Some patients may present with hematuria, polyuria, nocturia, hypertension and flank pain.(Padilla-Fernández et al., 2013)

Not only urinary abnormalities, but patients may also present with the other classic LN symptoms such as periorbital and peripheral edema.(Hashmi & Pandey, 2024) Other clinical features that might be present in LN patients are nausea, vomiting, and dyspnea. These symptoms associated with the high level of urine in blood or uremia.(Zemaitis et al., 2024) Anemia can be one of the sign that indicate that the patients is in the chronic phase of nephritis.(Khanna, 2011) On physical examination, patient may have anemic signs and pallor.(Hashmi & Pandey, 2024) In this case series, four out of five of the LN patient develop at least one of the classical sign and symptoms of LN. Only one patient in this case series that is not present with the classical sign and symptoms at all. Three out of five patients present with nausea and vomiting, and one patient presents with dyspnea. The symptoms clearly associated with the high level of urea because these three patients had quite high urea levels

compared to other patients. Only one of the patients in this case series presents with foamy urine and anemia. According to previous study, there's no consistent clinical and pathological relationship that can predict the severity of histological findings based on the clinical features of LN patients.(Wang et al., 2021)

Early identification for patients with lupus nephritis are essential to reduce the risks of irreparable kidney damage. Creatinine, blood urea, and glomerular filtration rate (GFR) measurement is important to evaluate kidney function in LN patient.(Bharti & Sinha, 2024) Creatinine and blood urea are elevated in LN patients while GFR may be low.(Kazi & Hashmi, 2024) Albumin also plays a significant role in determining the activity of SLE disease. Recent study has shown that hypoalbuminemia is correlated with active SLE and also can predict the risk of developing LN.(Liu et al., 2024) In this study, three out of five patients have an elevated serum creatinine, four out of five patients have a high blood urea level and only one patient present with normal eGFR while in other patients the eGFR are low. Another assessment that can predict the severity of LN is proteinuria assessment. Proteinuria was the protein level in urine. The result of proteinuria assessment can be negative, +1, +2, or +3.(Engli et al., 2018) High proteinuria indicates there is kidney damage in patients. In this case series, all patients present with proteinuria although not all the patients show urine abnormal features.

The type of renal involvement in SLE is important to determine the prognosis of LN patients. The most correct way to determine the type of kidney lesion is through pathological examination of kidney tissue.(Mok, 2012) From the kidney biopsy, LN classified into six standard classes.(Musa et al., 2024) In this study, three of five patients were diagnosed with LN Class II, while the others were diagnosed with LN Class IV-S (A) and Unclassified LN. Unclassified LN refers to cases that do not meet the criteria for any of the histopathology classes. This might happen because the kidney biopsy shows an atypical pattern, the biopsy sample might be inadequate either because of the sample size or the quality of the tissue, or the patient was in the early process of the disease. Prognosis of LN relies on the histopathology classes. Class I and class II have a good long-term prognosis. As the disease progresses, the prognosis worsens.(Musa et al., 2024) Particularly, the risks of end stage renal disease were high in patient with diffuse proliferative glomerulonephritis.(Mok, 2012)

CONCLUSION

In conclusion, the clinical features, laboratory, and histopathological profile in LN patients may vary depending on the onset of the disease. In the early process, LN may not present with specific clinical features and the histopathological findings can be atypical. This case series also shows that laboratory findings can be associated with the clinical features that are present in LN patients. The difficulty of making the diagnosis of LN in the early process requires more attention because it is important to improve the prognosis of LN.

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